

the full-length form of the BVH-3 polypeptide. SEQ ID NO:10 is the sequence of an antigenic fragment form of the BVH-3 polypeptide encoded by the 3' end of the BVH-3 gene. SEQ ID NO:16 is the sequence for the BVH-3 variant polypeptide from the SP63 strain. SEQ ID NO:55 is the sequence for the mature BVH-3 polypeptide. See, specification, *e.g.*, Table on page 37. Independent claims 16 and 25 have been amended to recite that the claimed "polypeptide elicits an antistreptococcal immune response in an individual when administered to the individual". Support for the recitation of the term "along the full length of the polypeptide is found in the specification, for example, on page 4, describing Figure 11:

Figure 11 depicts the comparison of the predicted amino acid sequences of the BVH-3 open reading frames from WU2, RX1, JNR.7/87, SP64, P4241 and A66 *S. pneumoniae* strains by using the program Clustal W from MacVector sequence analysis software (version 6.5). Underneath the alignment, there is a consensus where * and . characters indicate identical and similar residues, respectively.

An examination of Figure 11 shows that the comparison is along the full length of the 1019 amino acids of the BVH-3 polypeptide. Additional sequence alignments are shown in Dr. Hamel's Declaration, Figure 1 and Table 3, which show and summarize the results of the alignment along the length of amino acid residues 408 to 1039 (compare to the full length of SEQ ID 10, which extends from amino acids 512-1039, see specification, page 53, Table 3).

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Support for the recitation of the term "immune response" is found in the specification, *e.g.*, on pages 23, 41, 61 and 67. Support for the recitation of the term "antistreptococcal" is found in the specification, *e.g.*, on page 1, FIELD OF THE

INVENTION, and on page 7, discussing an immune response directed against *Streptococcus*. Support for the recitation of the term "protective" in claim 25 is found in the specification, e.g., pages 23 and 35. Support for the recitation of the term "individual" is found in the specification, page 27. Claim 25 is also amended to recite the use of adjuvants.

Claims 32-35 have been amended to depend from independent claims 16 and 25. New claims 38-42 are directed to preferred embodiments of the invention and are fully supported by the specification. New claim 38 is directed to the production of antistreptococcal antibodies in an individual. Support is found in the specification, e.g., pages 23 and 35. New claim 39 recites that the individual protected is a human, a mouse or a rat. Support is found in the specification, e.g., pages 27 and 36 for a human, pages 36 and 41 for a mouse, and page 36 for a rat. New claim 40 is directed to specific recited adjuvants. Support is found in the specification, page 26. New claims 41 and 42 are directed to polypeptides having at least 99% homology to the recited sequences. Support is found in the specification, page 24 and page 47.

Accordingly, claims 16, 18-20, 25, 32-35 and 38-42 are presented for examination on the merits. No new matter is added by these amendments to the claims.

The Examiner (Office Action of September 4, 2002, page 2, paragraph 5) has indicated that claims 18-20 would be allowable if rewritten to overcome the rejections under 35 U.S.C. § 112, second paragraph, as set forth in the Office Action, page 5, paragraph 18, rewriting to remove non-elected polypeptides. Applicants have rewritten the claims as suggested by the Examiner. Applicants submit that claims 18-20 are now allowable, without further discussion of the bases of the rejections discussed below.

I. Election/Restriction

The Examiner (Office Action of September 4, 2002, page 3, paragraph 5) has noted the constructive election of the claimed subject matter to certain polypeptides related by sequence to the polypeptide of SEQ ID NO:2, following Applicants' traverse. The Examiner indicated that claims 32-37 were being withdrawn from consideration.

Although Applicants continue to respectfully disagree with the basis of this restriction as being over-inclusive, Applicants have amended the claims to recite only four BVH-3 polypeptides that are related by sequence to the polypeptide of SEQ ID NO:2. SEQ ID NO:2 is the sequence for the full-length form of the BVH-3 polypeptide. SEQ ID NO:10 is the sequence of an antigenic fragment form of the BVH-3 polypeptide encoded by the 3' end of the BVH-3 gene. SEQ ID NO:16 is the sequence for the BVH-3 variant polypeptide from the SP63 strain. SEQ ID NO:55 is the sequence for the mature BVH-3 polypeptide.

Applicants respectfully reserve the right to prosecute the non-elected polypeptides in this or another patent application.

II. Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 16, 18-20 and 25 remain rejected under 35 U.S.C § 112, second paragraph, for the recitation of non-elected species, by the term "combinations thereof". Applicants have now amended claims 16, 18-20 and 25 to remove this term. Applicants respectfully request that this rejection be withdrawn.

Claim 32 remains rejected for alleged indefiniteness. The Examiner alleges that the metes and bounds of the claim are unclear. Applicants respectfully traverse.

"The essential inquiry pertaining to this requirement is whether the claims set out and circumscribe a particular subject matter with a reasonable degree of clarity and particularity. Definiteness of claim language must be analyzed, not in a vacuum, but in light of: (A) The content of the particular application disclosure; (B) The teachings of the prior art; and (C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made." MPEP § 2173.02. Here, the sequence of SEQ ID NOs: 2 have been provided in the figures (FIGURE 2, for example) and in the Sequence Listing. The size of the polypeptide is sufficient to raise an immune response (see, claim 16, from which claim 32 depends). The function of the polypeptide, as amended in claim 16, is to raise an immune response. Accordingly, the metes and bounds of the claim are clear.

Applicants respectfully request that this rejection be withdrawn.

III. Rejection Under 35 U.S.C. § 101

Claims 16, 25, 32 and 34-35 remain rejected under 35 U.S.C § 101 as allegedly lacking a specific, credible and substantial utility. Applicants respectfully disagree.

As previously put forth by the Applicants (Amendment and Reply, June 7, 2002), the claimed polypeptide is available as a marker of *Streptococcus* infection, or at the very least, a marker of the presence of contaminating bacteria in a sample. The specification also provides evidence that the claimed polypeptides are antigenic. The polypeptides were used to generate monoclonal antibodies that specifically bind to specified epitopes on the polypeptides of the invention. The specification also provides evidence of the successful use of the claimed polypeptides to elicit an effective

antistreptococcal immune response (Example 11, Tables 6 and 7). This disclosure is thus legally sufficient to show a utility that is specific to the claimed polypeptide.

Nevertheless, Applicants have now amended the independent claims 16 and 25 to recite that the claimed polypeptide elicits an antistreptococcal immune response in an individual when administered to the individual. As described above, support for this amendment is found in the specification as filed. Accordingly, the specification discloses the claimed invention and a utility specific to the claimed polypeptide.

In discussing the Amendment and Reply of June 7, 2002, the Examiner (Office Action of September 4, 2002, page 6) alleges that the Declaration of Dr. Josée Hamel is insufficient to overcome the rejection for alleged lack of specific utility. The Examiner alleges that the data presented in the declaration are derived from peptides having 99% identity to SEQ ID NO. 2, while the claims recite 95% identity. Applicants respectfully disagree.

Dr. Hamel's Declaration provides evidence that the claimed polypeptides having 95% identity to the recited sequences are useful.

Finally, it is my belief that changes to the amino acid sequence of the claimed fragments of SEQ ID NO. 2 of 5% or less will not alter immunogenicity of the claimed fragments in most cases. This is particularly true since the skilled artisan would recognize that conservative amino acid changes might be made, and the data indicate that specific regions of the fragments are not essential for immunogenicity. Moreover, the amino acid sequence of BVH-3 of 33 different strains show that these polypeptides differ from one another at several sites. Thus, the claimed polypeptide fragments can tolerate up to 5% amino acid changes and still elicit an immune response. Further, testing for immune response is routine in the art.

Declaration, page 4. See *also*, Declaration, Table 3, last column.

The word "at least 99% sequence similarity" in the Declaration, page 1, refer to Dr. Hamel's "understanding that the Examiner has rejected claims 16-20, which are directed to polypeptides having the specified sequence or polypeptides having at least 99% sequence similarity to the specified sequences, under 35 U.S.C. § 101". From a review of the Office Action of September 4, 2002, it appears that the Examiner has not yet accepted that a polypeptide having either 95% or 99% sequence identity would have specific utility. Applicants respectfully request reconsideration of Dr. Hamel's Declaration in its entirety.

Moreover, the Examiner (Office Action of September 4, 2002, page 6, paragraph 24) alleges that claims do not recite "the critical component of the C-terminal hyper variable region amino acid sequence which was taught as, and was shown to induce a protective immune response *in vivo*". Applicants respectfully disagree with the Examiner's characterization.

The specification discloses several polypeptides capable of eliciting an immune response. One of these polypeptides, BVH-3, SEQ ID NO:2, is similar to a partial polypeptide disclosed in published PCT application WO98/18930. See, specification, page 2; Dr. Hamel's Declaration, page 2, ("Prior to our reported results, no one had been able to identify the full-length BVH-3 gene, although others had tried and failed.") and Office Action of September 4, 2002, page 10, paragraph 3. The partial polypeptide of WO 98/18930 does not include the element recited in the claims of an ability to elicit an immune response. As shown in Dr. Hamel's Declaration, pages 6-7:

In regards to BVH-3, it is clear that prior to the filing of the present application, others had tried and failed to identify the full length gene. As a result, the cited reference, WO/18930, reports only partial sequences, which we have shown do not even encode polypeptide that confers immunity. It is noteworthy to mention that a stretch of 177 amino acid residues of the partial BVH-3 sequence reported by others is missing in some pneumococcal isolates (SEQ ID NO 15 and 16). Vaccination of animals with recombinant BVH-3 molecules of strain SP63 (SEQ ID NO 16) which lack the amino acids corresponding to residues 244 to 420 of sequence of strain SP64 (SEQ ID NO 2) and BVH-3 of strain SP64 conferred equivalent protection against experimental pneumococcal infection, thus indicating that the portion absent in SP63 sequence was not essential for protection.

Applicant has identified similarities in the polypeptides BVH-3 and BVH-11, in the N-terminal region corresponding to amino acids 1 to 225 in BVH-3 and 1 to 228 in BVH-11. By contrast, the C-terminal regions corresponding to amino acids 226 to 1039 from

BVH-3 and amino acids 229-840 from BVH-11 were found to be less similar. See, specification, page 48, EXAMPLE 7.

The term "hypervariable" is not a correct description of what the specification discloses about the BVH-3 sequence. What the specification instead discloses is sequence variation between the BVH-3 and BVH-11 polypeptides in their C-terminal regions. The sequence of the BVH-3 polypeptide is definite, not hypervariable, and is recited in the pending claims.

The specification discloses "These results suggest that BVH-3 and BVH-11 might share similar functions mediated by sequences present in the conserved region whereas BVH-3- and BVH-11-specific functions might be mediated by sequences in the divergent region." Specification, page 48, EXAMPLE 7. As is well known to those in the immunological arts, these differences in sequences would also suggest that the divergent, C-terminal regions could be more usefully immunogenic. Note the discussion of domains in the specification, page 47, EXAMPLE 6. See *also*, Dr. Hamel's Declaration. However, there is no suggestion that the BVH-3 sequence is hypervariable.

Applicants have discovered, disclosed and claimed a polypeptide that contains epitopes capable of eliciting an immune response and that is different in sequence from polypeptides shown in the prior art. This is legally sufficient for patentability. Applicants are not required to recite an allegedly "essential" element, when that element is not the subject matter which applicants regard as their invention. MPEP § 2172. Applicants again submit that an alignment of the amino acid sequences of BVH-3 of several different streptococcal strains shows that the claimed polypeptides can differ from one another at several sites (Figure 11 and Table 1 of the specification and Figure 1 of Dr.

Hamel's Declaration). Applicants' studies have provided sufficient information concerning the location of the immunogenic epitope to allow the skilled practitioner to make changes to the claimed polypeptides with a high expectation of successfully retaining immunogenicity. It follows therefore, that the claimed polypeptides can tolerate at least 5% amino acid sequence divergence, and still elicit an immune response. The recitation of allegedly "essential epitopes" are not legally required.

In summary, Applicants respectfully request that this rejection be withdrawn.

IV. Rejections Under 35 U.S.C. § 112, First Paragraph, Written Description

Claims 16, 25, 32 and 34-35 are rejected under 35 U.S.C § 112, first paragraph, as allegedly lacking sufficient written description in the specification. The Examiner (Office Action of September 4, 2002, page 8, paragraphs 29-30) alleges that the specification fails to provide a written description of polypeptides that have 95% sequence identity to SEQ ID NO. 2 in the absence of a specific biological activity. As described above, Applicants have amended the claims to recite that the biological activity of eliciting an immune response. Accordingly, this rejection is now moot and should be withdrawn.

V. Rejections Under 35 U.S.C. § 112, First Paragraph, Scope

Claims 25 and 34-35 are rejected under 35 U.S.C § 112, first paragraph, for alleged lack of enablement for the scope of the claims. The Examiner (Office Action of September 4, 2002, pages 9-10) also alleges that the specification only provides support for the use of the claimed polypeptide with the adjuvant QuilA. Applicants respectfully traverse. The specification discloses:

According to another aspect, there are provided vaccine compositions comprising one or more streptococcus polypeptides of the invention in admixture with a pharmaceutically acceptable carrier diluent or adjuvant. Suitable adjuvants include oils i.e. Freund's complete or incomplete adjuvant; salts i.e. $\text{AlK}(\text{SO}_4)_2$, $\text{AlNa}(\text{SO}_4)_2$, $\text{AlNH}_4(\text{SO}_4)_2$, silica, kaolin, carbon polynucleotides i.e. poly IC and poly AU. Preferred adjuvants include QuilA and Alhydrogel. Vaccines of the invention may be administered parenterally by injection, rapid infusion, nasopharyngeal absorption, dermoabsorption, or bucal or oral. Pharmaceutically acceptable carriers also include tetanus toxoid.

Vaccine compositions of the invention are used for the treatment or prophylaxis of streptococcus infection and/or diseases and symptoms mediated by streptococcus infection as described in P.R. Murray (Ed, in chief), E.J. Baron, M.A. Pfaller, F.C. Tenover and R.H. Tenover. *Manual of Clinical Microbiology*, ASM Press, Washington, D.C. sixth edition, 1995, 1482p which are herein incorporated by reference.

Specification, pages 26-27. Additional carriers, diluents and adjuvants are described in *Current Protocols in Immunology*, Edited by Coligan J.E. *et al.* (John Wiley & Sons Inc., New York), the entire contents of which are incorporated by reference in the specification, page 31. For example, a standard immunization protocol for the production of rabbit antibodies uses Freund's adjuvant (see, Cooper HM, Paterson Y. Production of Antibodies. *Current Protocols in Immunology*. Edited by Coligan J.E. *et al.* (John Wiley & Sons, 1992; Unit 2.4)). Additional carriers, diluents and adjuvants are disclosed in *Current Protocols in Immunology*, Unit 2, "Antibody Detection and Preparation". In addition, the specification, pages 41-42, EXAMPLE 3, shows the actual

use of DNA to elicit an immune response to *S. pneumoniae* antigens, clearly not in the presence of an adjuvant, specifically not QuilA.

Moreover, even if additional carriers had not been disclosed in the present specification, "that a claim may be broader than any specific example disclosed in the patent is of no moment." *Ralston Purina Co. v. Far-Mor-Co., Inc.*, 772 F.2d 1570, 1575 (Fed. Cir. 1985), citing *In re Rasmussen*, 650 F.2d 1212, 1215 (CCPA 1981). "The presence of only one working example should never be the sole reason for rejecting claims as being broader than the enabling disclosure, even though it is a factor to be considered along with all the other factors. To make a valid rejection, one must evaluate all the facts and evidence and state why one would not expect to be able to extrapolate that one example across the entire scope of the claims." MPEP § 2164.02. Here, there is nothing about the use of the QuilA adjuvant to suggest a peculiar interaction between the QuilA adjuvant and the polypeptides of the invention that would affect the ability to elicit an immune response. There is no reason to expect that the interaction between the QuilA adjuvant and the polypeptides of the invention would be any different than the interaction between the QuilA adjuvant and polypeptides related to BVH-11 and BVH-11-2, the use of which polypeptides in the immunization of mice is disclosed in the specification, pages 55-58, EXAMPLE 9. Thus, there is no reason to expect that the immunization results cannot be extrapolated across the entire scope of the claims to include carriers, diluents or adjuvants other than QuilA.

Indeed, Applicants submit that adjuvants disclosed in the specification would be expected by one of skill in the art to be useful components of the claimed vaccine composition. It is well known in the field that explicitly disclosed aluminum-based

adjuvants, such as the adjuvant Alhydrogel, can be used as a vaccine component to elicit an immune response. Aluminum is the only adjuvant universally licensed for use in humans. It is known that aluminium adjuvants used in mice have been shown to induce a T helper type 2 (Th₂)-based immune response, which selects for production of primarily IgG₁ subclass antibodies, while saponin-based adjuvants such as QuilA have been shown to induce a Th₁-based immune response, which directs the production of IgG_{2a} antibody in the mouse. Thus, both kinds of adjuvants can be used to elicit immune responses and both kinds of immune responses produce IgG antibodies. In humans, there is less demarcation between the kind of adjuvant used and the kind of immune response generated. Accordingly, one of skill in the art would expect that the adjuvants explicitly disclosed in the specification would be useful vaccine components for use in mice, and would have even better expectations that adjuvants would be useful vaccine components for use in humans. One of skill in the art could readily confirm the comparability of the different adjuvants using standard vaccination protocols and without undue experimentation.

Applicants respectfully request that this rejection be withdrawn.

VI. Rejections Under 35 U.S.C. § 102(a)

Claim 32 has been rejected under 35 U.S.C. § 102(a) over published PCT application WO 98/18930, which discloses a partial amino acid sequence of the mature BVH-3 polypeptide, Human Genome Science disclosure of SEQ ID NO.182, 56 and 66 (Office Action of September 4, 2002, page 6, paragraph 23, and page 10, paragraphs 33 and 34). Applicants respectfully traverse.

WO 98/18930 does not anticipate the claimed invention because each and every element as set forth in the claim is not found in WO 98/18930. See, MPEP § 2131. As described above, Applicants have amended the claims to recite that the claimed polypeptides elicit an immune response. This element is not found in WO 98/18930. The prior art fragment falls within the region of the BVH-3 polypeptide shown by Applicants to lack immunity inducing capability. See, Dr. Hamel's Declaration.

Also, as stated in the Amendment and Reply of June 7, 2002, the present invention is directed to polypeptides having specified amino acid sequences or having at least 95% sequence similarity to the recited sequences. The claimed polypeptides are thus, not anticipated by the disclosure of a different fragment of BVH-3 than claimed or amino acid sequences sharing less than 95% sequence identity with the claimed polypeptides.

Applicants respectfully request that the rejection under 35 U.S.C. § 102(a) be withdrawn.

It is respectfully submitted that the present application is in condition for allowance, an early notification thereof being earnestly solicited. If any issues remain outstanding, the Examiner is respectfully requested to contact the undersigned attorney so that prosecution of this application may be expedited.

To the extent necessary, please charge any shortage in fees due, including extension of time fees, to Deposit Account 500417 and please credit any excess fees to such account.

Respectfully submitted,

McDERMOTT, WILL & EMERY

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

16. (Amended) An isolated polypeptide having at least 95% identity along the full length of a second polypeptide, with a said second polypeptide having an amino acid sequence of any one of SEQ ID NOs: ~~2, 4, 6, 8, 10, 14, 16, 55 to 75, 77 to 79, 81 or 83~~ 2, 10, 16 or 55, wherein said isolated polypeptide elicits an antistreptococcal immune response in an individual when administered to the individual.
18. (Amended) An isolated polypeptide having an amino acid sequence of any one of SEQ ID NOs: ~~2, 4, 6, 8, 10, 14, 16, 55 to 75, 77 to 79, 81 or 83~~ 2, 10, 16 or 55.
19. An isolated polypeptide according to claim 18, wherein the N-terminal methionine residue of the polypeptide is deleted.
20. An isolated polypeptide according to claim 18, wherein the secretory amino acid sequence of the polypeptide is deleted.

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25. (Amended) A vaccine composition comprising a polypeptide having at least 95% identity along the full length of a second polypeptide with a said second polypeptide having an amino acid sequence of any one of SEQ ID NOs: ~~2, 4, 6, 8, 10, 14, 16, 55 to 75, 77 to 79, 81 or 83~~ 2, 10, 16 or 55, or a combination thereof wherein said polypeptide elicits a protective antistreptococcal immune response in an individual when administered to the individual, and a pharmaceutically acceptable ~~carrier, diluent or~~ adjuvant.
32. (Amended) ~~An~~ The isolated polypeptide of claim 16, said isolated polypeptide having an amino acid sequence of any one of SEQ ID NOs: ~~2, 10, 55, 58, 64, 65 or 66~~ 2, 10, 16 or 55.
33. (Amended) A The vaccine composition of claim 25, comprising a said polypeptide having an amino acid sequence of ~~SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:10, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:55, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:77, SEQ ID NO:78, and SEQ ID NO:79~~ any one of SEQ ID NOs: 2, 10, 16 or 55.
34. (Amended) A The vaccine composition according to ~~of~~ claim 25, wherein the polypeptide lacks an N-terminal methionine residue.

35. (Amended) A The vaccine composition ~~according to~~ of claim 25, wherein the secretory amino acid sequence of the polypeptide is deleted.
36. (Canceled) An isolated polypeptide having at least 95% identity with a second polypeptide comprising an amino acid sequence of any of one of SEQ ID NOs. 10, 58, 64, 65, and 66.
37. (Canceled) A vaccine composition comprising a polypeptide having at least 95% identity with a second polypeptide having an amino acid sequence of any of one of SEQ ID NOs. 10, 58, 64, 65, and 66 or a combination thereof.
38. (New) The isolated polypeptide of claim 16, wherein the immune response comprises the production of antistreptococcal antibodies by the individual.
39. (New) The isolated polypeptide of claim 16, wherein the individual is a human, a mouse or a rat.
40. (New) The vaccine composition of claim 25, wherein the carrier, diluent or adjuvant is selected from the group consisting of Freund's complete adjuvant, Freund's incomplete adjuvant, $\text{AlK}(\text{SO}_4)_2$, $\text{AlNa}(\text{SO}_4)_2$, $\text{AlNH}_4(\text{SO}_4)_2$, silica, kaolin, carbon polynucleotides, QuilA and Alhydrogel.

41. (New) The isolated polypeptide of claim 16, said polypeptide having at least a 99% identity along the full length of said second polypeptide.
42. (New) The vaccine composition of claim 25, said polypeptide having at least a 99% identity along the full length of said second polypeptide.